

## **REMARKS**

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Office Action dated December 27, 2010. In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

### **Status of the Claims**

As outlined above, claims 1-16, 18-20, 22-24 and 62-64 are pending in this application, wherein claim 23 has been amended and claims 2-5 and 18-20 have previously been withdrawn from consideration. This listing of claims will replace all prior versions, and listings, of claims in the application.

### **Oath/Declaration**

The oath or declaration was indicated as allegedly being defective and a new oath or declaration was indicated as being required, in compliance with 37 C.F.R. § 1.67(a). Contemporaneously submitted with this response is an Application Data Sheet which addresses the issues raised in the Office Action with regard to the previously submitted declaration. In view of the now submitted Application Data Sheet, Applicants respectfully request that the objection to the declaration be withdrawn.

### **Claim Rejections: 35 U.S.C. § 112**

#### **Claim 23**

Claim 23 was rejected under 35 U.S.C. § 112, second paragraph, for allegedly not having antecedent basis for the limitation “the cancer.” By this Amendment, Applicants have amended claim 23 to now recite “wherein the [cancer is] telomerase negative tumor cells are osteosarcoma, breast carcinoma, ovarian carcinoma, lung carcinoma, adrenocortical carcinoma or melanoma cells. Accordingly, Applicants respectfully request that the rejection to claim 23 be withdrawn.

### **Claim Rejections: 35 U.S.C. § 103**

#### **Claims 1, 2, 6-16, 22-24 and 62-64**

Claims 1, 2, 6-16, 22-24 and 62-64 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Woo et al. (U.S. Patent No. 5,631,236), as evidenced by Bryan et al. (2000, Nat. Med., v.3:1271-4 (of record, item CV on 09/09/2008 IDS) (“Woo”). Contrary to this rejection, Applicants respectfully submit that claims 1, 2, 6-16, 22-24 and 62-64 are not obvious in view of the aforementioned prior art references, which will be apparent from a review of the current claims, and in view of the following discussion.

The present invention is directed to a novel, non-obvious method for treating an individual suffering from cancer using an inhibitor or antagonist which blocks lengthening of telomerase in telomerase negative cells. Accordingly, the present method is specifically directed to treating telomerase negative cancer cells. The present inventors have discovered that by using a therapeutically effective amount of a composition comprising an inhibitor or antagonist of the first transcriptase encoded by L-1 (LINE-1) retrotransposon in telomerase negative cells, i.e. cells having alternative lengthening of telomeres, one can block lengthening of the telomeres in these telomerase negative cells. One exemplary, non-limiting example of an inhibitor is ganciclovir.

Features which are unique in the present method are the use of an inhibitor which blocks lengthening of telomeres in telomerase negative cells which does not require the use of a gene therapy approach. This is readily apparent and inherent from the claimed method, which is recited as treating lengthening of telomeres in telomerase negative cells, which does not have a limitation of the need for a gene therapy approach. Moreover, the present specification fully provides evidence that the claimed method, sans any gene therapy approach, is effective in blocking lengthening of telomeres in telomerase negative cells. Therefore, the present method provides for the treatment of individuals with telomerase negative cells, without use of gene therapies which conventionally have been used to treat telomerase negative cells. For a further discussion on conventional approaches using gene therapy, please see the discussion to follow.

Applicants respectfully submit that one of ordinary skill in the art would not have modified the method of Woo, which is specifically directed to a gene therapy method comprising a series of specific steps and administration of specific compounds to arrive at the claimed method, which in no way is a gene therapy method.

Woo discloses a gene therapy method for treating solid tumors, papilloma or warts *in vivo* using an adenoviral vector. The method disclosed by Woo necessarily requires the introduction of a recombinant adenoviral vector containing the herpes simplex virus-thymidine kinase (HSVTK) gene into a tumor. Subsequently, a prodrug (ganciclovir) is administered. The enzyme encoded by the HSVTK gene then converts the prodrug into a toxic compound. Thus, Woo is about gene-directed enzyme prodrug therapy. Woo focuses on delivering HSVTK to tumors using viral vectors in order to convert ganciclovir into a toxic intermediate and cause death in dividing cells. While the approach taught by Woo works through disruption of DNA synthesis, a process which is particularly active in cancer cells, Woo clearly discloses that the delivery of a prodrug converting enzyme, and expression of the enzyme, are necessary prerequisites for ganciclovir to become a toxic metabolite and kill tumor cells, i.e. to be an effective treatment.

Woo does not teach or suggest a method of treating solid tumors or cancers from telomerase negative cells with ganciclovir without the delivery of prodrug converting enzyme gene and expression of the gene, i.e. without the use of the gene therapy approach. Woo does not teach or in any way make obvious that L1RT is involved in the lengthening of telomeres in cancer cells and a nucleoside analog (e.g., ganciclovir) is an inhibitor of this enzyme, and that ganciclovir can block the lengthening of telomeres in telomerase negative cells. Therefore, one of ordinary skill in the art would not have been led to use ganciclovir, let alone any other inhibitor or reverse transcriptase encoded by L-1 to block telomere lengthening in telomerase negative cells, as claimed.

The Examiner points to Bryan as evidence showing that ALT<sup>+</sup> cells are telomerase negative. However, Bryan does not teach or in any way make obvious that L1RT is involved in the lengthening of telomeres in telomerase negative cancer cells and ganciclovir is an inhibitor of this enzyme, and that ganciclovir can block the lengthening of telomeres in telomerase negative cells. Therefore, one of ordinary skill in the art would not have been led to use ganciclovir, let alone any other inhibitor or reverse transcriptase encoded by L-1 to block telomere lengthening in telomerase negative cells, as claimed.

In rejecting the claims, the Examiner noted that “[a]ccording to the instant specification, cells exhibiting ALT depend on L1RT for elongating or maintaining telomeres (see paragraph spanning pages 9 and 10). Thus, ALT cells are understood to have L1RT activity.” See, the

sentence bridging pages 4-5 of the Office Action. However, that portion is part of the Applicants' description of the present invention. That knowledge was not within the level of ordinary skill in the art at the time the claimed invention was made. The Examiner relied on the Applicants' description of the invention (i.e. the hindsight knowledge) to establish a *prima facie* case of obviousness. The prior art does not contain or suggest that knowledge. To draw on hindsight knowledge of the patented invention is to use the invention as a template for its own reconstruction, which is an inappropriate process by which to determine patentability.

However, the use of ganciclovir or any other nucleoside analog without gene therapy to treat cancers, much less ALT cancers, was not an identified and predictable solution. Stated otherwise, there is no suggestion in the prior art for using ganciclovir or other nucleoside analogs without the HSVTK expression to treat an individual suffering from cancer with cells that are telomerase positive or, as in the instant invention, telomerase negative cells showing alternative lengthening of telomeres in the cells, and in so using there is no reasonable expectation of success. This is because, at the time of the present invention, it was known in the art that the TK enzyme is not usually found in mammalian cells and that toxic derivatives of nucleoside analogs were not found in cells infected with TK-deficient HSV strain.

**Thymidine kinase from herpesvirus** is a sub-family of thymidine kinases.<sup>12</sup> Its presence in herpesvirus-infected cells is used to activate a range of antivirals against herpes infection, and thus specifically target the therapy towards infected cells only. Such antivirals include:

- Purine analogues of guanine: Aciclovir, Famciclovir, Ganciclovir, Penciclovir, Valaciclovir, Valganciclovir

### References

1. Champness JN, Bennett MS, Wien F, *et al.* (August 1998). "Exploring the active site of herpes simplex virus type-1 thymidine kinase by X-ray crystallography of complexes with aciclovir and other ligands". *Proteins* **32** (3): 350–61. doi:10.1002/(SICI)1097-0134(19980815)32:3<350::AID-PROT10>3.0.CO;2-8. PMID 9715911.
2. Brown DG, Visse R, Sandhu G, Davies A, Rizkallah PJ, Melitz C, Summers WC, Sanderson MR (October 1995). "Crystal structures of the thymidine kinase from herpes simplex virus type-1 in complex with deoxythymidine and ganciclovir". *Nat. Struct. Biol.* **2** (10): 876–81. doi:10.1038/nsb1095-876. PMID 7552712.

See also, for example, Example 5 at column 5, lines 15-35 of Woo, noting that

...the mice were divided into two groups. In one group AD/.beta.D-gal was injected into the tumor and in the other group AD/HSV-TK was injected into the tumor. After about 1-2 weeks, half the mice in each group were treated with PBS and the other half were treated with ganciclovir. Only the mice treated with ganciclovir and AD/HSV-TK showed tumor regression.

Thus, it is clear from Woo that the delivery of HSVTK to tumors is essential to convert ganciclovir into a toxic intermediate and cause death in dividing cells.

The Applicants' claimed invention has nothing to do with the delivery and expression of HSV-TK and Woo does not teach or suggest a method without the use of HSV-TK for the treatment of cancers. A person of ordinary skill in the art would not have had a reasonable expectation of treating an individual suffering from osteosarcoma cancer by orally administering to the individual a therapeutically effective amount of a composition containing ganciclovir, without the expression of HSV-TK, based on what the entire disclosure of Woo conveys to one skilled in the art. Based on the teachings of Woo and/or Bryan, one skilled in the art cannot reasonably expect that ganciclovir can inhibit the activity of reverse transcriptase encoded by L-1 (LINE-1) retrotransposon in cells of the individual or can block the lengthening of telomeres in telomerase negative cells. Neither reference mentions that the reverse transcriptase encoded by L-1 (LINE-1) retrotransposon is involved in ALT in telomerase negative cells. Applicants respectfully point out that it is the invention, as a whole, and not some part of it, which must be obvious under 35 U.S.C. § 103(a).

The Examiner further alleges that "[i]t would have been obvious to administer two nucleoside analogs because Woo teaches several nucleoside analogs that can be used in the methods and one of skill in the art would reasonably expect that combining the use of two nucleoside analogs in the methods of Woo would result in equivalent if not better results than that achieved with a single nucleoside analog." Again, Applicants respectfully submit that Woo requires HSV-TK for a nucleoside analog to be toxic to a cancer cell. Woo is explicit in that the oral administration of ganciclovir and/or other nucleoside analogs alone is insufficient. The knowledge of one skilled in the art at the time of the Applicants' invention was that the other nucleoside analogs (e.g., AZT) also would have no effect on the telomere length in telomerase-negative cells (*see* Gan et al., 2002, FEBS Lett. 527:10-14). Therefore, the option of oral

administration of ganciclovir and/or other nucleoside analogs for inhibiting the activity of reverse transcriptase encoded by L-1 (LINE-1) retrotransposon and blocking the lengthening of telomeres in telomerase negative cells was not within the technical grasp of a person of ordinary skill in the art and that person has no good reason to pursue this option. The Examiner's conclusory allegations cannot be sustained in view of such evidence. Nevertheless, Applicants proceeded contrary to the art accepted wisdom, and achieved telomere shortening in telomerase negative cells and their growth inhibition by administering ganciclovir without a need for the HSV-TK gene therapy. Proceeding contrary to accepted wisdom in the art is itself evidence of non-obviousness. Furthermore, a person of ordinary skill, upon reading the Woo reference, would be led in a direction divergent from the path that was taken by the Applicants.

In view of the above discussion, the Examiner has not established that the combined teachings of the cited references would have suggested to one of ordinary skilled in the art that L1RT is involved in the lengthening of telomeres in cancer cells and ganciclovir is an inhibitor of this enzyme, and that ganciclovir can block the lengthening of telomeres in telomerase negative cells. The Examiner has not established a *prima facie* case of unpatentability.

Based on the foregoing, Applicants respectfully request that the rejection to the claims under 35 U.S.C. § 103(a) as being unpatentable over Woo, in view of Bryan, be withdrawn.

### **Double Patenting Rejection**

#### **Rejection in view of Co-pending Application No. 12/070,923 (hereinafter "the '923 application")**

Claims 1, 2, 6-16, 22-24 and 62-64 were provisionally rejected on the ground on non-statutory obviousness-type double patenting as being unpatentable over claims 59-85 of co-pending application no. 12,070,923. Contrary to this rejection, Applicants respectfully submit that, upon further consideration and review of the pending claims in view of the '923 claims, it will be found that the present claims are in no way obvious in view of the '923 claims. The presented claim recite novel and non-obvious subject matter which was not claimed in the '923 application.

Furthermore, since this is a provisional rejection, Applicants respectfully decline to take any further action at this time, including, but not limited to, filing a Terminal Disclaimer in the present application.

**Rejection in view of Co-Pending Application No. 11/920,668 (hereinafter “the ‘668 application”)**

Applicants respectfully submit that, upon further consideration of the present claims, in view of the ‘668 claims, it will be determined that the present claims present novel and non-obvious subject matter over the subject matter in the ‘668 application. Furthermore, since this is a provisional rejection, and the ‘668 application has not issued, such a rejection is premature and, therefore, Applicants respectfully decline taking any further action at this time, including, but not limited to, filing a Terminal Disclaimer in the present application.

**Rejection in view of Co-Pending Application No. 12,225,199 (hereinafter “the ‘199 application”)**

Applicants respectfully submit that, upon further consideration of the present claims, in view of the ‘199 claims, it will be determined that the present claims present novel and non-obvious subject matter over the subject matter in the ‘199 application. Furthermore, since this is a provisional rejection, and the ‘199 application has not issued, such a rejection is premature and, therefore, Applicants respectfully decline taking any further action at this time, including, but not limited to, filing a Terminal Disclaimer in the present application.

**Information Disclosure Statement (“IDS”)**

Finally, Applicants respectfully note that, in the Office Action, the Examiner has not formally acknowledged the IDS submitted in this case on September 9, 2008. However, the Office Action does refer to the IDS filed on September 9, 2008, applying reference “Woo,” as stated on page 4 in the 35 U.S.C. § 103(a) rejection. Applicants respectfully request that the IDS filed September 9, 2008 be acknowledged and the Examiner indicate that the references submitted were considered as listed on the PTO-1449 Form.

**Conclusion**

In light of the Amendments and Remarks, Applicants respectfully request early and favorable action with regard to the present application, and a Notice of Allowance for all pending claims is earnestly solicited.

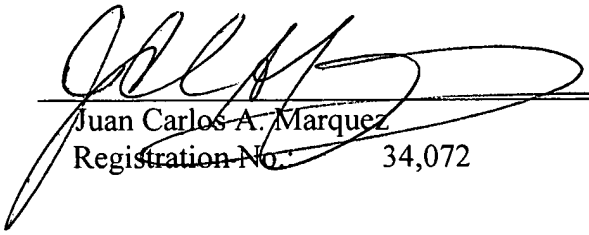
Should there be any outstanding issues requiring discussion that would further the prosecution and allowance of the above-captioned application, the Examiner is invited to contact the Applicant's undersigned representative at the address and telephone number indicated below.

Respectfully submitted,

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